Real-World Case Series Study of Spinal Muscular Atrophy Pediatric Patients Treated With Onasemnogene Abeparvovec (Zolgensma)

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Background

- Spinal muscular atrophy (SMA) is a rare neuromuscular genetic disease that in the most common form is fatal in early childhood.
- Approved in May 2019, onasemnogene abeparvovec-xioi (Zolgensma) became the only one-time gene therapy for SMA treatment in patients less than 2 years of age at a cost of over $2.1 million.[1,2]
- At the time of onasemnogene abeparvovec FDA approval, there were only 25 patients with high quality data reported.[2] The data was from a single-arm, open-label study design, lacking randomization or a control group with a median follow-up of 24 months.[3]
- Use of non-gene disease-modifying therapy (DMT), nusinersen (Spinraza) or risdiplam (Evrysdi), before gene therapy may be due to bridge therapy, waiting for adenovirus antibody titers to drop and/or needing time for health plan onasemnogene abeparvovec treatment approval.[4]
- Early identification of SMA through newborn screening and treatment before onset of clinical symptoms, ideally before 3 months of age, is associated with better developmental outcomes.[3]
- March 2024 findings from RESTORE, a prospective and observational registry, report event-free survival, defined as avoidance of death or permanent ventilatory support, for patients with two *survival motor neuron 2 (SMN2)* gene copies of 93.7% at Year 1, 90% at Year 2, and 100% for patients with three *SMN2* copies.[5]
- Real-world onasemnogene abeparvovec outcomes data are needed to assess effectiveness and durability.

Objective

To describe real-world SMA non-gene drug treatment and SMA disease-related outcomes in a cohort of members administered onasemnogene abeparvovec.

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Methods

- This study is a case series and descriptive analysis using integrated pharmacy and medical claims data from Prime Therapeutics' monthly membership averaging 1.5 million Medicaid and 16.5 million commercially insured members.
- Data obtained for this study included medical claims (date of service, diagnoses received, procedures performed, place of service, and drugs received), pharmacy claims (fill dates and National Drug Code [NDC] numbers), and eligibility information (patient demographics and enrollment history).
- Study inclusion was limited to members with a paid onasemnogene abeparvovec claim between June 1, 2019, and March 31, 2024 (Identification Period).
- Beginning with the study start date (June 1, 2017) or member's date of insurance enrollment (whichever occurred closest to infusion date), the member was followed before the onasemnogene abeparvovec infusion and after (posttreatment). The posttreatment follow-up went through the member's insurance disenrollment or end of study period (April 30, 2024), whichever occurred first, as shown in **Figure 1.**
- Key study outcomes of interest were type of SMA clinical management received, which included paid pharmacy claims for a non-gene disease-modifying treatment (DMT) of interest (i.e., nusinersen (Spinraza) or risdiplam (Evrysdi)), a medical claim with discharge status of death or hospice, or two or more medical claims separated by 30 or more days indicating respirator dependence or chronic respiratory failure, as shown in **Figure 2.**
  - Death or hospice medical claim discharge status codes.
    - → 20 = expired, 40 = expired at home, 41 = expired in medical facility (e.g., hospital, skilled nursing facility (SNF), intermediate care facilities (ICF), or free-standing hospice), 50 = hospice home, 51 = hospice – medical facility
  - International Classification of Diseases Version 10 (ICD-10) and Current Procedural Terminology (CPT) codes indicating dependence on respirator or chronic respiratory failure.
    - → Z99.11, Dependence on respirator [ventilator] status
    - → Z99.12, Encounter for respirator [ventilator] dependence during power failure
    - → J96.1, Chronic respiratory failure
    - → CPT 5A0955Z, Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours
- All member characteristics and study outcomes were descriptively summarized and stratified according to the year of onasemnogene abeparvovec infusion. Age at onasemnogene abeparvovec infusion was categorized based on 3 months of age (i.e., 3 months of age or younger, greater than 3 months of age). Pretreatment enrollment and posttreatment follow-up were summarized using median, minimum, and maximum values. All other measured data were reported using member counts and percentages based on total study member counts or total member counts according to year of infusion.
- Pre and posttreatment study outcomes were categorized into mutually exclusive groups according to study period and type of therapy received:
  - Pretreatment: No SMA therapy, nusinersen only, risdiplam only, risdiplam and nusinersen, ventilation only, ventilation plus nusinersen and/or risdiplam
  - Posttreatment: No SMA therapy, nusinersen only, risdiplam only, ventilation only

Table 1

Characteristics and outcomes of spinal muscular atrophy members treated with onasemnogene abeparvovec: June 2019 to April 2024

Characteristic	Total Study Period	Onasemnogene Abeparvovec Infusion Date (Year)					
	June 2019 to April 2024	2019	2020	2021	2022	2023	2024
Members with onasemnogene abeparvovec infusion, n (%)	52 (100)	6 (11.5)	10 (19.2)	13 (25)	8 (15.4)	13 (25)	2 (3.8)
Mean age (months) at time of onasemnogene abeparvovec infusion, min-max	7.2 (1-24)	21 (15-24)	5.6 (1-23)	8.8 (2-24)	5.75 (<1-16)	1.6 (<1-6)	6.5 (2-11)
Members 3 months of age or younger, n (%)	26 (50)	0 (0)	5 (50)	5 (39)	4 (50)	11 (85)	1 (50)
Members greater than 3 months of age, n (%)	26 (50)	6 (100)	5 (50)	8 (61)	4 (50)	2 (15)	1 (50)
Female, n (%)	30 (58)	4 (67)	5 (50)	9 (69)	4 (50)	8 (62)	0 (0)
Pretreatment Study Period							
Median enrollment time in months, min-max	2 (<1-23)	20.5 (15-23)	2 (<1-14)	2 (<1-20)	3 (<1-16)	1 (<1-5)	5.5 (1-10)
Members with non-gene DMT pharmacy claim, n (%)	14 (27)	4 (67)	2 (20)	1 (8)	4 (50)	2 (15)	1 (50)
Members with respirator dependence or chronic respiratory failure[1], n (%)	4 (8)	3 (50)	0 (0)	1 (8)	0 (0)	0 (0)	0 (0)
Posttreatment Study Period[2]							
Median follow-up in months, min-max	15 (1-56)	55 (27-56)	24 (1-50)	27 (1-38)	20.5 (5-25)	9 (3-15)	2 (1-3)
Members with non-gene DMT pharmacy claim, n (%)	2 (4)	0 (0)	0 (0)	2 (15)	0 (0)	0 (0)	0 (0)
Members with respirator dependence or chronic respiratory failure[1], n (%)	7 (13)	4 (67)	1 (10)	2 (15)	0 (0)	0 (0)	0 (0)
Members without pretreatment respirator dependence or chronic respiratory failure[3], n (%)	4 (8)	1 (17)	1 (10)	2 (15)	0 (0)	0 (0)	0 (0)
Members with medical claim indicating death or hospice as discharge status, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[1] 2+ medical claims occurring 30 or more days apart
[2] Members posttreatment follow-up period in months from infusion date to minimum of end of enrollment or end of study period
[3] Among members with outcome, claims indicating respiratory failure prior to onasemnogene abeparvovec
non-gene DMT = disease-modifying treatment consisted of risdiplam (Evrysdi) or nusinersen (Spinraza)

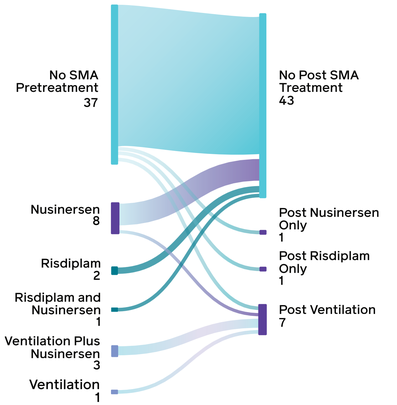
Figure 1

Study and measurement periods

Pretreatment period ends on day before onasemnogene abeparvovec infusion date and begins on the date (i.e. enrollment start, study start) closest to infusion date. Posttreatment measurement period is time from onasemnogene abeparvovec infusion date to insurance disenrollment or end of study period (4/30/2024), whichever occured first.

Figure 2

Spinal muscular atrophy management pre and post onasemnogene abeparvovec treatment



Ventilation defined as 2+ medical claims for respiratory dependence or chronic respiratory failure occurring 30 or more days apart.

Non-gene disease-modifying therapy (DMT) are nusinersen (Spinraza) or risdiplam (Evrysdi).

Results (Table 1 and Figure 2)

- During the 4.9-year assessment period, 52 onasemnogene abeparvovec-treated members were identified (42 [81%] commercial and 10 [19%] Medicaid). 58% were female.
- Mean age at time of onasemnogene abeparvovec infusion was 7.2 months and ranged from <1 month to 24 months. 26 (50%) out of 52 members were treated within 3 months of birth (mean age = 38 days). The average age among members treated after 3 months of birth was 13 months.
- In 2019, the mean age of members treated was 21 months compared to less than 2 months for those treated in 2023, the last full year in the member identification period.
- 14 members had prior non-gene DMT: 10 nusinersen only, 3 risdiplam only, and 1 both.
- Median posttreatment follow-up time was 15 months (min-max: 1 to 56 months).
- There were no claims for death or hospice in the posttreatment period.
- 7 members had posttreatment medical claims indicating respirator dependence and chronic respiratory failure.
  - 4 out of 7 members (57%) had medical claims indicating respirator dependence or chronic respiratory failure prior to onasemnogene abeparvovec treatment.
  - 5 out of 7 members (71%) were >3 months of age at date of onasemnogene abeparvovec.
  - 4 out of 7 (57%) used non-gene DMT prior to onasemnogene abeparvovec treatment.
- 2 members initiated non-gene DMT in the posttreatment period with neither member having claims indicating respirator dependence and chronic respiratory failure.
  - 1 member had 12 nusinersen claims beginning 18 months after onasemnogene abeparvovec.
  - 1 member had 4 claims for risdiplam beginning 13 months after onasemnogene abeparvovec.

Limitations

- Members' SMA type and number of *survival motor neuron 2 (SMN2)* gene copies were not available, and if available, would have allowed for stratification of results by type. Better motor milestones and longer survival are observed in patients with three compared to two copies of *SMN2* gene.[5]
- This study was retrospective in nature and data were sourced from administrative health care claims data. Claims data are subject to coding error and incompleteness; this could impact SMA clinical management assignment, resulting in misclassification bias as well as potentially missing mortality identification due to lack of death information comprehensively in the claims data.
- ICD-10 codes for respirator dependence are not specific to duration of mechanical ventilation support. Therefore, duration of respirator dependence was not reported as part of this study.
- This study did not assess the persistence of different types of SMA therapies assessed as part of our study measures. For example, members using non-gene DMT within 3 months prior to onasemnogene abeparvovec may be using non-gene DMT as a bridge to onasemnogene abeparvovec therapy or switching to onasemnogene abeparvovec. Therefore, this study may not be representative of all clinically relevant SMA treatment combinations that are associated with differences in clinical outcomes.[5,6]

Conclusions

- This real-world analysis of 52 members treated with onasemnogene abeparvovec, with a 15-month median follow-up (range 1 month to 56 months), found no evidence of death or hospice.
- 1 in 7 members had medical claims post onasemnogene abeparvovec, potentially indicating therapy failure, although 43% of members with posttreatment respiratory failure had respiratory failure evidence prior to onasemnogene abeparvovec.
- 1 in 13 members have post onasemnogene abeparvovec respiratory failure claims with no prior respiratory failure claims history and these members were all age 11.3 months or older when they received treatment. Respiratory failure may be intermittent in this population dependent upon concommitent conditions (e.g., infections, surgery). Claims data were not able to identify permanent ventilation.
- The decrease trend in age at onasemnogene abeparvovec treatment over the study period year observed in our analysis may be due to increased newborn screening. As of June 2021, 34 states offered SMA newborn screening, with all 50 states offering screening as of January 2024.[7,8]
- 1 in 26 initiated non-gene DMT with nusinersen or risdiplam, adding substantial cost at greater than $300,000 annually for most children, without clinical trial evidence to support use post onasemnogene abeparvovec treatment.
- These findings can aid in the development of evidence-based coverage decisions, understanding risk for future non-gene DMT therapy, and pharmaceutical manufacturer value-based contract negotiations.

References

1. FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality. U.S. Food & Drug Administration. Published May 24, 2019. Accessed August 14, 2024. https://www.fda.gov/news-events/press-announcements
2. Starner CI, Gleason PP. Spinal muscular atrophy therapies: ICER grounds the price to value conversation in facts. *J Manag Care Spec Pharm*. 2019;25(12):1306-1308 doi.org/10.18553/jmcp.2019.25.12.1306
3. Strauss, K. A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. *Nat Med*. 2022;28(7):1381-1389. doi.org/10.1038/s41591-022-01866-4.
4. Ferrante L., Melendez-Zaidi A, Lindsey W, Lotze T. Novel use of nusinersen as a therapeutic bridge to onasemnogene abeparvovec-xioi in a premature neonate with type 1 spinal muscular atrophy. *Muscle Nerve*. 2022;66(2):E8-E10. doi:10.1002/mus.27648
5. Servais L., Day JW, De Vivo DC, et al. Real-world outcomes in patients with spinal muscular atrophy treated with onasemnogene abeparvovec monotherapy: Findings from the RESTORE Registry. *J Neuromuscul Dis*. 2024;11(2):425-442. doi:10.3233/jnd-230122
6. Stettner GM, Hasselmann O, Tscherter A, Galiart E, Jacquier D, Klein A. Treatment of spinal muscular atrophy with onasemnogene abeparvovec in Switzerland: a prospective observational case series study. *BMC Neurol*. 2023;23(1):88. doi:10.1186/s12883-023-03133-6
7. Hale K, Ojodu J, Singh S. Landscape of spinal muscular atrophy newborn screening in the United States: 2018–2021. *Int J Neonatal Screen*. 2021;7(3):33. doi:10.3390/ijns7030033
8. Newborn screening for SMA. Cure SMA. Accessed August 29, 2024. https://www.curesma.org/newborn-screening-for-sma/